# Vitamin D in insulin sensitivity and obesity

# VALORIZATION

Obesity prevalence is increasing worldwide and often coincides with circulating vitamin D deficiency and whole-body insulin resistance. The present thesis describes how obesity-related phenotypes, vitamin D concentrations as well as vitamin D-related genes link to insulin resistance. The valorization potential of the work described in this thesis will be discussed in terms of societal and economic relevance, the implications for the scientific community and health care professionals, activities/products, including future planning and realization.

## Societal and Economic Relevance

Obesity is associated with type 2 diabetes mellitus, cardiovascular diseases (mainly heart disease and stroke), diabetes, musculoskeletal disorders (especially osteoarthritis – a highly disabling degenerative disease of the joints), some types of cancers, depression and a reduced quality of life (1), and more recently it was identified as a major risk factor for fatal COVID-19 (2). Obesity is a chronic metabolic disorder resulting from an energy imbalance, by which a long-term positive energy balance leads to the storage of excess energy as body fat (3). Furthermore, obesity is often characterized with vitamin D deficiency. Putative mechanisms, linking obesity, vitamin D, and insulin resistance are described in this thesis, including obesity, vitamin D deficiency, adipose tissue dysfunction, and tissue-specific insulin sensitivity.

Our study showed that the prevalence of vitamin D 25(OH)$D_3$ deficiency [based on Endocrine Society cut-off value < 50 nmol/L] in our study was about 45.7%, and BMI is the main determinant of vitamin D 25(OH)$D_3$ concentration in individuals with overweight/obesity (**chapter 4)**, indicating that obesity-associated vitamin D deficiency could be recognized as an important public health concern. Ensuring sufficient circulating vitamin D 25(OH)$D_3$ level is essential to maintain general health but also may be of importance in the management of obesity, and the prevention of insulin resistance and T2D.

Oral and intravenous vitamin D supplementation have been suggested to effectively increase circulating vitamin D 25(OH)$D_3$ level. Our meta-analysis showed that vitamin D supplementation is an effective means to increase circulating vitamin D 25(OH)$D_3$ level, despite substantial heterogeneity (**chapter 6**). However, more research is needed to study the efficacy and bioavailability of different types (and routes of administration) of vitamin D supplementation to more effectively increase serum vitamin D levels in overweight/obesity.

We did not find any associations between circulating vitamin D levels with hepatic, muscle, and adipose tissue insulin sensitivity assessed by hyperinsulinemic-euglycemic clamp (**chapter 4**). Furthermore, our meta-analysis showed no beneficial effect of vitamin D supplementation on the improvement of insulin sensitivity (**chapter 6**), suggesting no direct causality between vitamin D deficiency and whole body and tissue specific insulin resistance in human obesity.

Our study using arterio-venous difference techniques across abdominal subcutaneous adipose tissue (SAT) showed that there was an impaired release of active vitamin D metabolite in obese men (**chapter 3**). In addition, we observed that VDR expression in abdominal SAT is increased in obesity and associated with adipose tissue insulin sensitivity

**(chapter 4**). This may suggest that adipose tissue may be a key target organ to improve vitamin D metabolism in the context of human obesity. Furthermore, currently a project on exercise-mediated Vitamin D mobilization sequestered in the human adipose tissue (Vita-DEx project) is ongoing (4). If exercise might be beneficial to mobilize vitamin D from adipose, then this may have implications regarding the management/treatment of a low vitamin D status in obesity.

## Scientific Community

The content of the chapters in this thesis have been presented at national scientific meetings (i.e. NASO spring meeting and ADDRM meeting) and international conferences (The 25$^{th}$ and 26$^{th}$ European Congress on Obesity). The results have also been discussed to health professionals and colleagues inside and outside the scientific community with the purpose to discuss the medical and societal consequences of obesity and vitamin D deficiency. Moreover, the studies described in this thesis have been published or will become available to the scientific community through publication in peer-reviewed journals.

The findings presented in this thesis, may be of value for health care professionals (e.g. physicians and dieticians). Given that fact that the incidence of vitamin D deficiency is considerable high (>40%) among obese individuals, this may possibly have consequences for recommended nutritional intake. However, a recent RCT reported 750 g/week of salmon was not sufficient to prevent a decrease in serum 25-hydroxyvitamin D [25(OH)$D_3$] in autumn in South-Western Norway in adults with overweight/obesity (5). These data suggest that increasing vitamin D intake from diet only, may not be adequate to improve circulating vitamin D 25(OH)$D_3$ level in obese individuals. Furthermore, although Vitamin D supplementation increased circulating vitamin D levels 25(OH)$D_3$ levels, nevertheless, this did not translate to improved whole-body insulin sensitivity (**chapter 6**). Therefore, a combination mode of interventions (e.g. exercise and nutrition) and more personalized strategies should be explored in future research.

## Activities/Products and Innovation

In this thesis, we combined state-of-the-art methodology including: hyper-insulinemic-euglycemic clamp, adipose tissue gene expression using qRT-PCR , plasma vitamin D and vitamin D fluxes analysis using gold standard LC/MS-MS measurement, adipose tissue blood flow measurements (i.e. xenon washout technique), arterio-venous balance technique, PCR-based genetic variant analysis in combination with subcutaneous adipose tissue transcriptomic, which together gave important insights in obesity related vitamin D metabolism. Furthermore, we have also conducted a systematic review and meta-analysis in this thesis, providing one of the highest levels of evidence in human clinical research to date.

## Planning and Realization

The causal relationship between vitamin D and obesity related metabolic health is still under debate. Although, from studies described in this thesis, the direct link between vitamin D

and overall metabolic health (non-skeletal function) may not be mediated by tissue-specific insulin signaling/sensitivity pathways. However, the link between Vitamin D and metabolic health may be partly mediated via its effects on gut microbiota composition/diversity and gut health (6). This is supported by the presence of VDR expression in human enterocytes and from a recent genome wide association study that suggests a potential link between VDR variants and gut microbiota diversity (7). However, future studies are needed to investigate in more detail the relationship between vitamin D, gut microbiota, gut health, and its effects on host metabolic health.

Results from this thesis should encourage future Vitamin D research, for instance, how genetic variants (**chapter 5**) in vitamin D metabolisms (VDR and CYP) may influence the metabolic outcome of vitamin D supplementation. This will pave the way for studies with more personalized (sub-group, i.e. carrier and non-carriers of VDR SNPs) approaches. In addition, combining vitamin D supplementation with other modes of intervention (i.e. exercise / dietary intervention induced weight loss) might provide new strategies towards a more personalized approach for obesity related vitamin D deficiency treatment.

Last but not least, while obesity has been suggested as one of the major comorbidities of covid-19 (2), vitamin D deficiency is a common feature in obesity, and may also be a determinant of covid-19 outcome. More studies warrant to explore the link between vitamin D deficiency, obesity, and covid-19 which is highly relevant given the current pandemic our society and scientific community is dealing with.

**References:**

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